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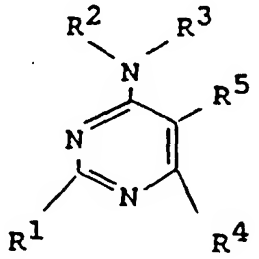
(54) **Substituted Pyrimidine Derivatives, Process for the Synthesis Thereof and Use Thereof As a Tool**

(57) Pyrimidine derivatives of formula I



I

where R^1, R^2, R^3, R^4 and R^5 have the given meanings, their salts and a process for synthesis thereof are described. Because of their sorbitol-accumulating activity, they are suitable for use as a tool in the pharmacological screening model for aldose reductase inhibitors.

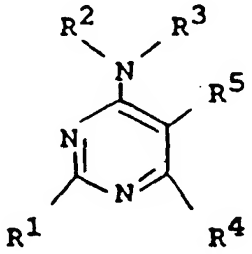
Substituted Pyrimidine Derivatives, Process for the Synthesis Thereof and Use Thereof As a Tool

Increased intracellular sorbitol concentrations are regarded as the cause of delayed diabetic sequelae such as retinopathy, neuropathy and nephropathy. Sorbitol is formed to an increased extent by the enzyme aldose reductase at elevated blood glucose levels. The accumulation of sorbitol can be prevented by aldose reductase inhibitors.

Screening for aldose reductase inhibitors (ARI) is performed on streptozocin-diabetic rats. The animals are used in the ARI screening one to two weeks after induction of diabetes with 60 mg streptozocin sulfate per kg per rat. The reduction in the elevated sorbitol content in red blood cells, nerves and the lens of the eye 5-6 hours after treatment with the aldose reductase inhibitors to be tested is used as a measure of the efficacy of ARIs.

Streptozocin is a carcinogen. Therefore, the streptozocin must be administered and the animals maintained after administration (2-3 days) under biohazardous conditions. Urine excreted during the first two days after administration of streptozocin must be disposed of as special wastes, and the contaminated boxes require special cleaning. However, not only is streptozocin carcinogenic and toxic to beta cells, it also causes liver and kidney damage. Therefore, the animals are not used in the ARI screening until 10-14 days after administration of the substance.

It has now surprisingly been found that pyrimidine derivatives of formula I



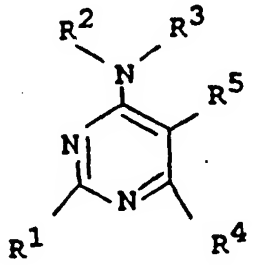
I

and their pharmacologically tolerable salts, when administered orally or parenterally, acutely and chronically, cause an intracellular increase in sorbitol without any effect on blood glucose. The increase in sorbitol induced by the pyrimidine derivatives of formula I is prevented by simultaneous treatment with aldose reductase inhibitors. Therefore, these sorbitol-accumulating pyrimidine derivatives are suitable for new, simplified, less time-consuming and less expensive acute screening for aldose reductase inhibitors on normal nondiabetic rats.

By induction of functional and morphological changes in the sense of delayed diabetic sequelae in animals treated chronically with pyrimidine derivatives of formula I, e.g., by administration in drinking water, it can also be demonstrated that intracellular accumulation of sorbitol is in fact the direct cause of the delayed diabetic sequelae.

Parameters for delayed diabetic sequelae include: nerve conduction velocity, dilation of pupils, retina capillary aneurysms, thickness of the basal membrane of the capillaries.

Therefore, the present invention relates to pyrimidine derivatives of formula I:



I

where

R^1, R^4 and R^5 may be the same or different and denote hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, (C_1-C_6) alkoxy, (C_6-C_{12}) aryl or amino, R^2 and R^3 may be the same or different and denote hydrogen, (C_1-C_6) alkyl, (C_6-C_{12}) aryl or (C_6-C_{12}) aralkyl with 1 to 4 alkyl carbons, or R^2 and R^3 together with the nitrogen to which they are attached form an azetidino, pyrrolidino, piperidino, piperazino or morpholino group, or an azetidino, pyrrolidino, piperidino, piperazino or morpholino group substituted with the same or different R^6 and R^7 groups, where R^6 and R^7 denote (C_1-C_6) alkylsulfamoyl,* N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, (C_1-C_6) alkoxycarbonyl, N,N-(C_1-C_4)-dialkylcarbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, (C_6-C_{12})-arylcarbamoyl substituted in the aryl moiety with (C_1-C_6) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3 substituted (C_6-C_{12}) arylcarbamoyl, carbamoyl, (C_1-C_6) alkylcarbonyl, (C_6-C_{12}) arylcarbonyl, (C_6-C_{12}) arylcarbonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_1-C_6) alkylsulfonyl, (C_1-C_6) alkylsulfinyl, (C_6-C_{12}) arylsulfonyl, (C_6-C_{12}) arylsulfonyl, heteroarylcarbonyl or heteroarylsulfonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, or one of the R^6 or R^7 substituents is hydrogen, as well as their physiologically tolerable salts.

* Original German text reads: "(C_1-C_6) alkyl, sulfamoyl," which is unlikely.—*The Language Service.*

In the definitions given above and below, alkyl and alkoxy (including those in derived groups) stand for linear or branched groups, halogen stands for fluorine, chlorine, bromine and iodine, in particular for chlorine.

Heteroaryl is understood to refer to an unsubstituted heteroaryl group having an oxygen atom or 1 to 3 nitrogens as heteroatom(s). (C_6-C_{12}) aryl may be, for example, phenyl, naphthyl or biphenyl.

Pyrimidine derivatives of formula I are preferred, where
R^1, R^4 and R^5 may be the same or different and denote hydrogen or (C_1-C_6) alkyl, and
R^2 and R^3 together with the nitrogen to which they are attached form a piperazine ring, which is optionally substituted by the same or different R^6 and R^7 groups, where
R^6 and R^7 denote (C_1-C_6) alkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, (C_1-C_6) alkoxycarbonyl, N,N-(C_1-C_4)-dialkylcarbamoyl, N-(C_1-C_4)-alkylcarbamoyl, carbamoyl, (C_1-C_6) alkylcarbonyl, (C_6-C_{12}) arylcarbonyl, (C_6-C_{12}) arylcarbonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_1-C_6) alkylsulfonyl, (C_1-C_6) alkylsulfinyl, (C_6-C_{12}) arylsulfonyl, (C_6-C_{12}) arylsulfonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, or they may denote a heteroarylcarbonyl or heteroarylsulfonyl, or one of the R^6 or R^7 substituents is hydrogen, as well as their physiologically tolerable salts.

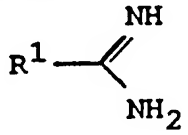
Especially preferred are pyrimidine derivatives of formula I, where
R^1, R^4 and R^5 may be the same or different and denote hydrogen or (C_1-C_4) alkyl, and
R^2 and R^3 together with the nitrogen to which they are attached form a piperazine ring that may optionally have another R^6 substituent in position 4, where
R^6 denotes sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-(C_1-C_4)-dialkylcarbamoyl, (C_1-C_6)-alkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_6-C_{12}) arylcarbonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, or pyridinecarbonyl, as well as their physiologically tolerable salts.

Most especially preferred are pyrimidine derivatives of formula I, where
R^1 denotes hydrogen or (C_1-C_2) alkyl, especially methyl,
R^4 denotes hydrogen or (C_1-C_2) alkyl, especially hydrogen,
R^5 is hydrogen,
R^2 and R^3 together with the nitrogen to which they are attached form a piperazine ring that may optionally have another R^6 substituent in position 4, where R^6 is N-(C_1-C_3)-alkylsulfamoyl, N,N-(C_1-C_2)-dialkylsulfamoyl, N-(C_1-C_2)-alkylcarbamoyl, N,N-(C_1-C_2)-dialkylcarbamoyl, (C_1-C_2)-

alkylcarbonyl, phenylcarbonyl, optionally substituted in the phenyl moiety with (C_1-C_2) alkyl, chloro or NO_2, or pyridinecarbonyl, especially N,N-dimethylsulfamoyl, phenylcarbonyl or pyridinecarbonyl, as well as their physiologically tolerable salts.

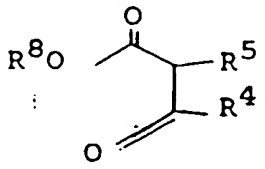
This invention also relates to a method of synthesis of compounds of formula I, which is characterized in that, in otherwise known manner,

a) a compound of formula II



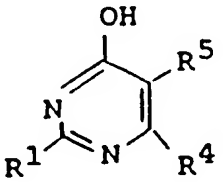
II

where R^1 has the meanings indicated for formula I or its acid addition salt, is reacted with a compound of formula III



III

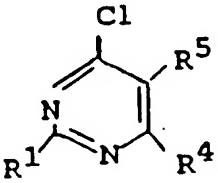
where R^4 and R^5 have the meanings indicated for formula I, and R^8 is methyl or ethyl, or with the base salt thereof to yield a compound of formula IV



IV

where R^1, R^4 and R^5 have the meanings indicated for formula I;

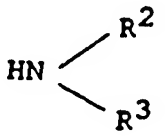
b) a resulting compound IV is reacted with an inorganic acid chloride such as phosphorus oxychloride, to yield a pyrimidine derivative of formula V



V

where the R^1, R^4 and R^5 groups have the meanings indicated for formula I;

c) a resulting compound of formula V is reacted with an amine of formula VI



VI

where R^2 and R^3 have the meanings indicated for formula I, to yield a compound of formula I; and

d) optionally a resulting compound of formula I, where one or both of the substituents R^2 and/or R^3 denotes hydrogen, is converted to a compound where R^2 and/or R^3 have the meanings indicated for formula I, with the exception of hydrogen;

e) optionally the R^6 and/or R^7 groups is/are introduced into a resulting compound of formula I, where R^2 and R^3 together with the nitrogen atom to which they are attached form the azetidino, pyrrolidino, piperidino, piperazino or morpholino group; and

f) optionally a resulting compound of formula I is converted to a physiologically tolerable salt.

The method according to this invention is carried out analogously to the methods described in the literature (cf., for example, D.J. Brown, *The Chemistry of Heterocyclic Compounds, The Pyrimidines, Suppl. I* (1970), *Suppl. II* (1985), Wiley Interscience, N.Y. and the literature cited therein).

Reacting compounds of formula V with ammonia (formula VI, $R^2 = R^3 = H$) or primary amines (formula VI, $R^2 = H$, $R^3 \neq H$) yields compounds of formula I where $R^2 = R^3 = H$ or $R^2 = H$, $R^3 \neq H$, and wherein the (remaining) hydrogen atoms may optionally be replaced by reaction with compounds $Z\text{-}R^2/Z\text{-}R^3$, where Z denotes chlorine, bromine or iodine, and R^2 and R^3 have the meanings indicated for formula I, except for hydrogen.

Reacting compounds of formula V with amines of formula VI, where R^2 and R^3 together with the nitrogen to which they are attached form a ring system, yields compounds of formula I, where the ring system either already has the R^6 and R^7 substituents, as defined above, or is unsubstituted. If this ring system still has acid hydrogen atoms, as in piperazine, for example, they may optionally be substituted by reaction with compounds $Z\text{-}R^6/Z\text{-}R^7$, where Z is chlorine, bromine or iodine and R^6 and/or R^7 has the meanings indicated for formula I.

Compounds of formula I can be converted to their physiologically tolerable salts by reaction with acids.

The compounds according to this invention provoke functional symptoms along the lines of a diabetic neuropathy by intracellular accumulation of polyol without a diabetic metabolic condition.

Pharmacological Investigation

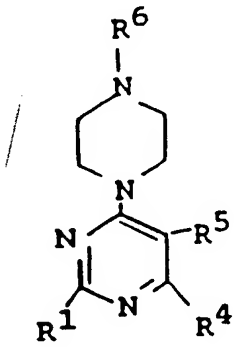
When the compounds according to the present invention are administered orally to the rat in doses of 5-50 mg/kg, they cause a dose-dependent increase in sorbitol concentration in the sciatic nerve and in the red blood cells of normal and streptozocin-diabetic rats within 4 to 5 hours.

After oral administration of the compound according to Example 1d in a dose of 25 mg/kg of rat, a sorbitol level corresponding to that found in streptozocin-diabetic rats after 8 days is reached in the aforementioned tissues of normal rats after 4 to 5 hours. By simultaneous oral treatment with the ARI spiro-2,7-difluoro-9H-fluorene-9,4-imidazolidine-2,5-dione (= HOE 843), the increase in sorbitol is prevented in a dose-dependent manner.

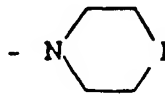
On the basis of the ability to induce an accumulation of sorbitol, the compounds according to this invention are suitable especially as a tool in the pharmacological model for testing aldose reductase inhibitors. This invention therefore also relates to this use of the pyrimidine derivatives of formula I and their pharmacologically tolerable salts. In addition to the compounds listed in the examples, the compounds of general formula I listed in the following table and their salts may also be obtained.

Abbreviations used: methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), hexyl (Hex), acetyl (Ac), phenyl (Ph), iso (i) and cyclo (c).

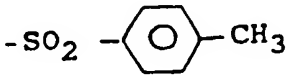
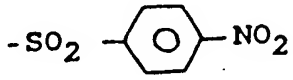
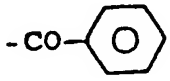
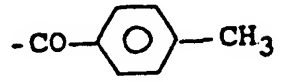
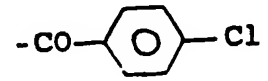
Table



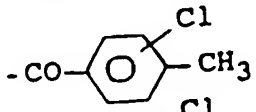
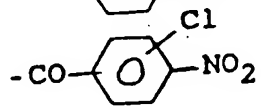
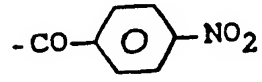
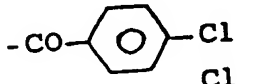
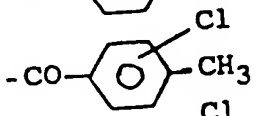
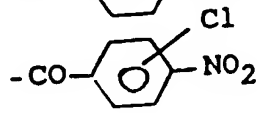
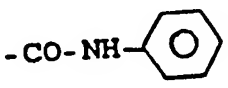
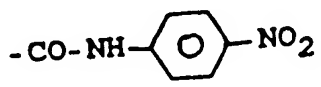
(Formula I with R^2 R^3 =



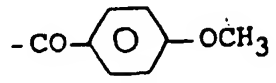
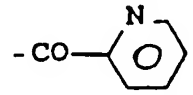
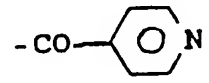
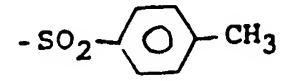
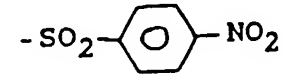
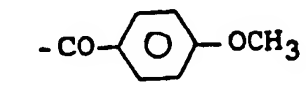
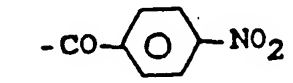
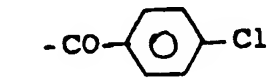
)

R^1	R^4	R^5	R^6
H	H	H	H
H	H	H	
H	H	H	
H	H	H	$-SO_2-CH_3$
H	H	H	$-SO_2-N(Me)_2$
H	H	H	$-SO_2-NHCH_3$
H	H	H	
H	H	H	$-CO-CH_3$
H	H	H	
H	H	H	
H	H	H	
H	H	H	$-SO_2-N(Et)_2$

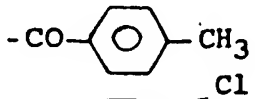
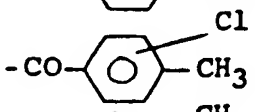
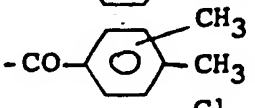
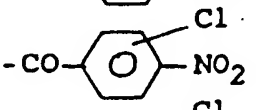
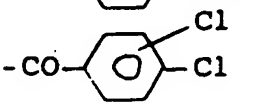
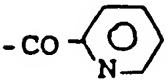
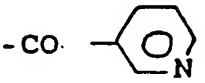
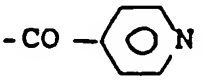
Continuation of table

R^1	R^4	R^5	R^6
H	H	H	$-SO_2-N(iPr)_2$
H	H	H	
H	H	H	
H	H	H	$-CO-NHEt$
CH_3	H	H	H
CH_3	H	H	$-SO_2-NHCH_3$
CH_3	H	H	
CH_3	H	H	
CH_3	H	H	
CH_3	H	H	
CH_3	H	H	
CH_3	H	H	$-SO_2-N(Et)_2$
CH_3	H	H	$-CO-CH_3$
CH_3	H	H	$-CO-N(Me)_2$
CH_3	H	H	
CH_3	H	H	

Continuation of table

R^1	R^4	R^5	R^6
CH_3	H	H	
CH_3	H	H	
CH_3	H	H	
Et	H	H	H
Et	H	H	
Et	H	H	
Et	H	H	$-SO_2-CH_3$
Et	H	H	$-SO_2-NH(CH_3$
Et	H	H	$-SO_2-N(CH_3)_2$
Et	H	H	$-SO_2-NEt_2$
Et	H	H	$-SO_2-N(iPr)_2$
Et	H	H	$-SO_2—Et$
Et	H	H	$-COCH_3$
Et	H	H	
Et	H	H	
Et	H	H	

Continuation of table

R^1	R^4	R^5	R^6
Et	H	H	
Et	H	H	
Et	H	H	
Et	H	H	
Et	H	H	
Et	H	H	
Et	H	H	
Et	H	H	

The following examples serve to illustrate this invention without thereby limiting its scope in any way:

Example 1

2-Methyl-4-(4-N,N-dimethylsulfamoylpiperazino)pyrimidine and the corresponding hydrochloride

a) 4-Hydroxy-2-methylpyrimidine

A suspension of 240 g of sodium hydride (55% suspension) in 5 liters of toluene was mixed dropwise at room temperature with a mixture of 555 g of ethyl formate and 440 g of ethyl acetate while stirring until the evolution of hydrogen was concluded. Stirring was continued for one hour, the precipitate was filtered out with suction and washed with ether, yielding 650 g of sodium ethyl formyl acetate that was dissolved in 4 liters of water and reacted with 475 g of acetamidine hydrochloride. The reaction solution was left to stand for 2 days at room temperature, then the water was distilled off in vacuo and the residue was chromatographed over silica gel, yielding 240 g of 4-hydroxy-2-methylpyrimidine (melting point 214°C).

b) 4-Chloro-2-methylpyrimidine

11 g of 4-hydroxy-2-methylpyrimidine was reacted with 50 mL of phosphorus oxychloride and heated slowly to 80°C. After the solids had dissolved completely, excess phosphorus oxychloride was distilled off in vacuo and the residue was poured onto ice. The aqueous phase was extracted several times with dichloromethane, the organic phases were dried over sodium sulfate, filtered and concentrated.

This yielded 8 g of 4-chloro-2-methylpyrimidine (melting point 59°C).

c) 2-Methyl-4-piperazinopyrimidine

13 g of 4-chloro-2-methylpyrimidine was dissolved in 200 mL of tetrahydrofuran and mixed with 17.5 g of piperazine. The reaction mixture was heated at reflux for 24 hours. The precipitated piperazine hydrochloride was filtered out with suction and washed with tetrahydrofuran. After concentrating the solution in vacuo, 19 g of 2-methyl-4-piperazinopyrimidine was obtained and was reacted without further purification.

d) 2-Methyl-4-(4-N,N-dimethylsulfamoylpiperazino)pyrimidine

5 g of 2-methyl-4-piperazinopyrimidine was dissolved in 80 mL of pyridine and mixed with 4.7 g of N,N-dimethylamidosulfonyl chloride at room temperature. The reaction solution was heated for 5 hours at 50°C. After the starting compound had dissolved completely, the reaction mixture was combined with diethyl ether after cooling to room temperature. The precipitated crystals were filtered with suction. After purification by column chromatography, 2.6 g of 2-methyl-4-(4-N,N-dimethylsulfamoylpiperazino)pyrimidine was obtained (melting point 114°C).

e) 2-Methyl-4-(N,N-dimethylsulfamoylpiperazino)pyrimidine hydrochloride

1 g of 2-methyl-4-(N,N-dimethylsulfamoylpiperazino)pyrimidine was dissolved in 5 mL of methanol and mixed with 10 mL of methanolic hydrochloric acid at room temperature while stirring. After 15 minutes, the solvent was distilled off in vacuo and the residue was mixed with acetone. 1 g of hydrochloride was isolated as white crystals (melting point 238°C, with decomp.).

Example 2

2-Methyl-4-(4-benzoylpiperazino)pyrimidine

1 g of 2-methyl-4-piperazinopyrimidine was dissolved in 50 mL of acetone and mixed with 2 g of potassium carbonate and 0.8 g of benzoyl chloride. The suspension was heated at reflux for 6 hours, until none of the starting compound could be detected. After filtration, the filtrate was concentrated in vacuo and the residue was recrystallized from dichloromethane/petroleum ether, yielding 0.5 g of 2-methyl-4-(4-benzoylpiperazino)pyrimidine (melting point 147°C).

The following compounds were synthesized in similar manner:

Example 3

2-Methyl-4-(4-ethylcarbamoylpiperazino)pyrimidine (melting point 138°C)

Example 4

2-Methyl-4-(4-methanesulfonylpiperazino)pyrimidine (melting point 241°C, with decomp.)

Example 5

2-Methyl-4-[4-(4-nitrobenzenesulfonyl)piperazino]pyrimidine (melting point 166°C)

Example 6

2-Methyl-4-[4-(p-toluenesulfonyl)piperazino]pyrimidine (melting point 142°C)

Example 7

2-Methyl-4-(4-nicotinoylpiperazino)pyrimidine (melting point 118°C)

Example 8

6-Methyl-4-(4-benzoylpiperazino)pyrimidine (melting point 132°C)

Example 9

6-Methyl-4-[4-(p-toluenesulfonyl)piperazino]pyrimidine (melting point 221°C)

Example 10

6-Methyl-4-(4-nicotinoylpiperazino)pyrimidine (melting point 78°C)

Example 11

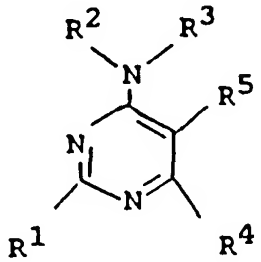
6-Methyl-4-(4-N,N-dimethylsulfamoylpiperazino)pyrimidine (melting point 107°C)

Example 12

6-Methyl-4-(4-methanesulfonylpiperazino)pyrimidine (melting point 198°C)

Claims

1. Pyrimidine derivatives of formula I



I

where
R^1 , R^4 and R^5 are the same or different and denote hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, (C_1-C_6) alkoxy, (C_6-C_{12}) aryl or amino, R^2 and R^3 are the same or different and denote hydrogen, (C_1-C_6) alkyl, (C_6-C_{12}) aryl or (C_6-C_{12}) aralkyl with 1 to 4 alkyl carbons, or R^2 and R^3 together with the nitrogen to which they are attached form an azetidino, pyrrolidino, piperidino, piperazino or morpholino group, or an azetidino, pyrrolidino, piperidino, piperazino or morpholino group substituted with the same or different R^6 and R^7 groups, where R^6 and R^7 denote (C_1-C_6) alkylsulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, (C_1-C_6) alkoxycarbonyl, N,N-(C_1-C_4)-dialkylcarbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, (C_6-C_{12})-

arylcarbamoyl substitued in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, substituted (C_6-C_{12}) arylcarbamoyl, carbamoyl, (C_1-C_6) alkylcarbonyl, (C_6-C_{12}) arylcarbonyl, (C_6-C_{12}) arylcarbonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_1-C_6) alkylsulfonyl, (C_1-C_6) alkylsulfinyl, (C_6-C_{12}) arylsulfonyl, (C_6-C_{12}) arylsulfonyl, heteroarylcarbonyl or heteroarylsulfonyl, substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3 or one of the R^6 or R^7 substituents is hydrogen, as well as their physiologically tolerable salts.

2. Pyrimidine derivatives according to Claim 1 and their physiologically tolerable salts, characterized in that in formula I at least one of the substituents has the following meaning:
R^1, R^4 and R^5 (same or different) denote hydrogen or (C_1-C_6) alkyl, and
R^2 and R^3 together with the nitrogen to which they are attached form a piperazine ring, that is optionally substituted by the same or different R^6 and R^7 groups, where
R^6 and R^7 denote (C_1-C_6) alkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, (C_1-C_6) alkoxycarbonyl, N,N-(C_1-C_4)-dialkylcarbamoyl, N-(C_1-C_4)-alkylcarbamoyl, carbamoyl, (C_1-C_6) alkylcarbonyl, (C_6-C_{12}) arylcarbonyl, (C_6-C_{12}) arylcarbonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_1-C_6) alkylsulfonyl, (C_1-C_6) alkylsulfinyl, (C_6-C_{12}) arylsulfonyl, (C_6-C_{12}) arylsulfonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, or they may denote a heteroarylcarbonyl or heteroarylsulfonyl, or one of the R^6 or R^7 substituents is hydrogen.

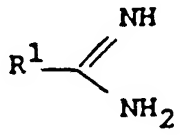
3. Pyrimidine derivatives according to Claim 1 and their physiologically tolerable salts, characterized in that at least one of the substituents in formula I has the following meaning:
R^1, R^4 and R^5 (same or different) denote hydrogen or (C_1-C_4) alkyl, and
R^2 and R^3 together with the nitrogen to which they are attached form a piperazine ring that may optionally have another R^6 substituent in position 4,
R^6 denotes sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-(C_1-C_4)-dialkylcarbamoyl, (C_1-C_6)-alkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_6-C_{12}) arylcarbonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, or pyridinecarbonyl.

4. Pyrimidine derivatives according to Claim 1 and their physiologically tolerable salts, characterized in that at least one of the substituents in formula I has the following meaning:
R^1 denotes hydrogen or (C_1-C_2) alkyl, especially methyl,
R^4 denotes hydrogen or (C_1-C_2) alkyl, especially hydrogen,
R^5 denotes hydrogen,

R^2 and R^3 together with the nitrogen to which they are attached form a piperazine ring that may optionally have another R^6 substituent in position 4, where R^6 is N-(C_1-C_3)-alkylsulfamoyl, N,N-(C_1-C_2)-dialkylsulfamoyl, N-(C_1-C_2)-alkylcarbamoyl, N,N-(C_1-C_2)-dialkylcarbamoyl, (C_1-C_2)-alkylcarbonyl, phenylcarbonyl, optionally substituted in the phenyl moiety with (C_1-C_2) alkyl, chloro or NO_2, or pyridinecarbonyl, especially N,N-dimethylsulfamoyl, phenylcarbonyl or pyridinecarbonyl.

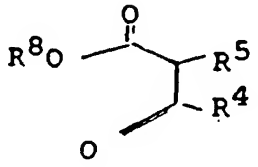
5. Method of synthesis of compounds of formula I according to Claim 1, characterized in that, essentially by otherwise known methods,

a) a compound of formula II



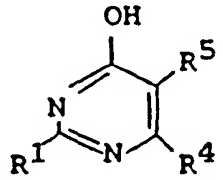
II

where R^1 has the meanings indicated for formula I or its acid addition salt, is reacted with a compound of formula III



III

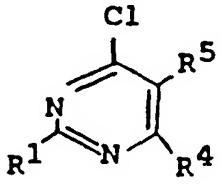
where R^4 and R^5 have the meanings indicated for formula I, and R^8 is methyl or ethyl, or with the base salt thereof to yield a compound of formula IV



IV

where R^1, R^4 and R^5 have the meanings indicated for formula I;

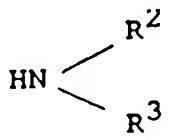
b) a resulting compound IV is reacted with an inorganic acid chloride such as phosphorus oxychloride to yield a pyrimidine derivative of formula V



V

where R^1, R^4 and R^5 groups have the meanings indicated for formula I;

c) a resulting compound of formula V is reacted with an amine of formula VI



VI

where R^2 and R^3 have the meanings indicated for formula I, to yield a compound of formula I; and

d) optionally a resulting compound of formula I, where one or both R^2 and/or R^3 substituents is hydrogen, is converted to a compound where R^2 and R^3 have the meanings indicated for formula I, with the exception of hydrogen;

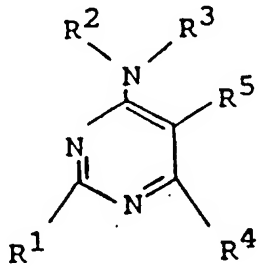
e) optionally the $R^6$and/or R^7 groups is/are introduced into a resulting compound of formula I, where R^2 and R^3 together with the nitrogen atom to which they are attached form the azetidino, pyrrolidino, piperidino, piperazino or morpholino group, and

f) optionally a resulting compound of formula I is converted to a physiologically tolerable salt.

6. Use of compounds of formula I according to Claim 1 and their salts as a tool in the pharmacological model.

Claims for the following convention country: Spain

1. Method of synthesis of pyrimidine derivatives of formula I



I

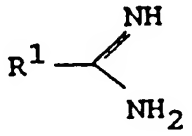
where

R^1 , R^4 and R^5 are the same or different and denote hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6) alkyl, (C_1-C_6) hydroxyalkyl, (C_1-C_6) alkoxy, (C_6-C_{12}) aryl or amino,

R^2 and R^3 are the same or different and denote hydrogen, (C_1-C_6) alkyl, (C_6-C_{12}) aryl or (C_6-C_{12}) aralkyl with 1 to 4 alkyl carbons, or R^2 and R^3 together with the nitrogen to which they are attached form an azetidino, pyrrolidino, piperidino, piperazino or morpholino group, or an azetidino, pyrrolidino, piperidino, piperazino or morpholino group substituted with the same or

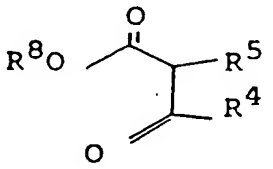
different R^6 and R^7 groups, where R^6 and R^7 denote (C_1-C_6) alkylsulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, (C_1-C_6) alkoxycarbonyl, N,N-(C_1-C_4)-dialkylcarbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, (C_6-C_{12}) arylcarbamoyl substituted in the aryl moiety with (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, halogen, NO_2, NH_2, CN or CF_3, substituted (C_6-C_{12}) arylcarbamoyl, carbamoyl, (C_1-C_6) alkylcarbonyl, (C_6-C_{12}) arylcarbonyl, (C_6-C_{12}) arylcarbonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_1-C_6) alkylsulfonyl, (C_1-C_6) alkylsulfinyl, (C_6-C_{12}) arylsulfonyl, (C_6-C_{12}) arylsulfonyl heteroarylcarbonyl or heteroarylsulfonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3 or one of the R^6 or R^7 substituents is hydrogen, as well as their physiologically tolerable salts, characterized in that

a) a compound of formula II



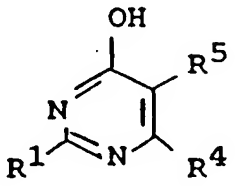
II

where R^1 has the meanings indicated for formula I or its acid addition salt, is reacted with a compound of formula III



III

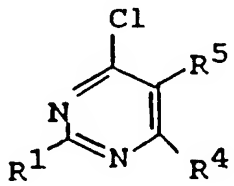
where R^4 and R^5 have the meanings indicated for formula I, and R^8 is methyl or ethyl, or with its base salt to yield a compound of formula IV



IV

where R^1, R^4 and R^5 have the meanings indicated for formula I;

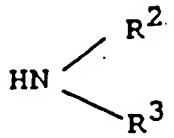
b) a resulting compound IV is reacted with an inorganic acid chloride to yield a pyrimidine derivative of formula V



V

where the R^1, R^4 and R^5 groups have the meanings indicated for formula I;

c) a resulting compound of formula V is reacted with an amine of formula VI



VI

where R^2 and R^3 have the meanings indicated for formula I, to yield a compound of formula I; and

d) optionally a resulting compound of formula I, where one or both of the substituents R^2 and/or R^3 is hydrogen, is converted to a compound where R^2 and/or R^3 have the meanings indicated for formula I, except for hydrogen;

e) optionally the R^6 and/or R^7 groups is/are introduced into a resulting compound of formula I, where R^2 and R^3 together with the nitrogen atom to which they are attached form the azetidino, pyrrolidino, piperidino, piperazino or morpholino group, and

f) optionally a resulting compound of formula I is converted to a physiologically tolerable salt.

2. Method according to Claim 1, characterized in that a compound [of] formula I, where at least one of the substituents in formula I has the following meaning:
R^1, R^4 and R^5 (the same or different) denote hydrogen or (C_1-C_6) alkyl, and
R^2 and R^3 together with the nitrogen to which they are attached form a piperazine ring, which is optionally substituted by the same or different R^6 and R^7 groups, where
R^6 and R^7 denote (C_1-C_6) alkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, (C_1-C_6) alkoxycarbonyl, N,N-(C_1-C_4)-dialkylcarbamoyl, N-(C_1-C_4)-alkylcarbamoyl, carbamoyl, (C_1-C_6) alkylcarbonyl, (C_6-C_{12}) arylcarbonyl, (C_6-C_{12}) arylcarbonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, (C_1-C_6) alkylsulfonyl, (C_1-C_6) alkylsulfinyl, (C_6-C_{12}) arylsulfonyl, (C_6-C_{12}) arylsulfonyl, heteroarylcarbonyl or heteroarylsulfonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, or one of the R^6 or R^7 substituents is hydrogen, or its physiologically tolerable salts are synthesized.

3. Method [according to] Claim 1, characterized in that a compound of formula I, where at least one of the substituents has the following meaning:
R^1, R^4 and R^5 (same or different) denote hydrogen or (C_1-C_4) alkyl, and

R^2 and R^3 together with the nitrogen to which they are attached form a piperazine ring that may optionally have another R^6 substituent in position 4,
R^6 denotes sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-(C_1-C_4)-dialkylsulfamoyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-(C_1-C_4)-dialkylcarbamoyl, (C_1-C_6) alkylcarbonyl, (C_6-C_{12}) arylcarbonyl, (C_6-C_{12}) arylcarbonyl substituted in the aryl moiety with (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halogen, NO_2, NH_2, CN or CF_3, or pyridinecarbonyl, or its physiologically tolerable salts are synthesized.

4. Method according to Claim 1, characterized in that a compound of formula I, where at least one of the substituents has the following meaning:
R^1 denotes hydrogen or (C_1-C_2) alkyl, especially methyl,
R^4 denotes hydrogen or (C_1-C_2) alkyl, especially hydrogen,
R^5 is hydrogen,
R^2 and R^3 together with the nitrogen to which they are attached form a piperazine ring that may optionally have another R^6 substituent in position 4, where R^6 is N-(C_1-C_3)-alkylsulfamoyl, N,N-(C_1-C_2)-dialkylsulfamoyl, N-(C_1-C_2)-alkylcarbamoyl, N,N-(C_1-C_2)-dialkylcarbamoyl, (C_1-C_2) alkylcarbonyl, phenylcarbonyl, optionally substituted in the phenyl moiety with (C_1-C_2) alkyl, chloro or NO_2, or pyridinecarbonyl, especially N,N-dimethylsulfamoyl, phenylcarbonyl or pyridinecarbonyl or its physiologically tolerable salts are synthesized.

5. Use of compounds of formula I according to Claim 1 and their salts as a tool in the pharmacological model.

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EUROPEAN SEARCH REPORT

Number of Application

EP 90 10 3186

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document, with indication, where appropriate, of the relevant passage	Relevant to claim	CLASSIFICATION OF APPLICATION (Int. Cl. 5)
X	JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS No. 24, 1976, pages 1060, 1061; J. H. FORSBERG et al.: "Infrared Spectroscopic Evidence for the Formation of an Intermediate Involved in the Zeolite-catalysed [reaction?] of n-Butenes upon Addition of Sulphur Dioxide" * page 1061, left column, compounds (1) *	1–4	C 07 D 239/42 A 61 K 49/00
X	JOURNAL OF ORGANIC CHEMISTRY vol. 52, 1987, pages 1017-1021; J. H. FORSBERG et al.: "Use of Lanthanide (III) Ions as Catalysts for the Reactions of Amines with Nitriles" * page 1081, compounds 6a-6f *	1–4	
X	German Patent No. 2,149,249 B (PFIZER INC.) * Claim 1; column 3, lines 1-27 *	1, 5	
X	German Patent No. 1,695,975 A (UCB) * Claim 1 *	1	
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The foregoing search report was drawn up for all patent claims.

Site of search	Closing date of search	Examiner
BERLIN	May 17, 1990	HASS, C.V.F.

CATEGORY OF CITED DOCUMENTS:

X : Of particular importance considered by itself.
Y : Of particular importance in connection with another publication of the same category.
A : Technological background
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Category	Citation of document, with indication, where appropriate, of the relevant passage	Relevant to claim	CLASSIFICATION OF APPLICATION (Int. Cl. 5)
X	British Patent No. 2,198,132 A (L'OREAL) * Claims 1, 2 *	1	
X	German Patent No. 2,152,742 A (SHIONOGI AND CO. LTD.) * Claims 1, 4-9 *	1	
X	British Patent No. 959,699 A (MAY AND BAKER LTD.) * Page 2, lines 6-18 *	5	
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